Can we predict the outcome for people with patellofemoral pain? A systematic review on prognostic factors and treatment effect modifiers.

AUTHORS
Matthews M[1], Rathleff MS[2,3], Claus A[1], McPoil T[4], Nee R[5], Crossley K[6] and Vicenzino B[1]

[1] The University of Queensland, School of Health and Rehabilitation Sciences, Sports Injuries Rehabilitation and Prevention for Health research unit, CCRE Spine, Brisbane, Australia
[2] Research Unit for General Practice in Aalborg and Department of Clinical Medicine, Aalborg, Denmark
[3] SMI, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Aalborg, Denmark
[4] School of Physical Therapy, Rueckert-Hartman College for Health Professions, Regis University, Denver, USA
[5] School of Physical Therapy, Pacific University, Hillsboro, USA
[6] La Trobe University, La Trobe Sport and Exercise Medicine Research Centre, Melbourne, Australia

ADDRESS FOR CORRESPONDENCE
Prof Bill Vicenzino, The University of Queensland, School of Health and Rehabilitation Sciences, Sports Injuries Rehabilitation and Prevention for Health research unit, CCRE Spine, Brisbane, Australia
Email: b.vicenzino@uq.edu.au

KEYWORDS:
Anterior knee pain, patient characteristics, clinical prediction rules, non-operative management

RUNNING TITLE
Predicting outcomes for people with patellofemoral pain

WORD COUNT (4500 limit): 4406

ABSTRACT
Background: Patellofemoral pain is a multifactorial and often persistent knee condition. One strategy to enhance patient outcomes is using clinically assessable patient characteristics to predict the outcome and match a specific treatment to an individual
Aim: A systematic review was conducted to determine which baseline patient characteristics were i) associated with patient outcome (prognosis); or ii) modified patient outcome from a specific treatment (treatment effect modifiers).
Methods: Six electronic databases were searched (July 2016) for studies evaluating the association between those with patellofemoral pain, their characteristics and outcome. All studies were appraised using the Epidemiological Appraisal Instrument. Studies that aimed to identify treatment effect modifiers underwent a checklist for methodological quality.
Results: The 24 included studies evaluated 180 participant characteristics. Twelve studies investigated prognosis, and 12 studies investigated potential treatment effect modifiers. Important methodological limitations were identified. Some prognostic studies used a retrospective design. Studies aiming to identify treatment effect modifiers often analysed too many variables for the limiting sample size and typically failed to use a control or comparator treatment group. Sixteen factors were reported to be associated with a poor outcome, with longer duration of symptoms the most reported (>4months). Preliminary evidence suggests increased midfoot mobility may predict those who have a successful outcome to foot orthoses.
Conclusion: Current evidence can identify those with increased risk of a poor outcome, but methodological limitations make it difficult to predict the outcome after one specific treatment compared to another. Adequately designed randomised trials are needed to identify treatment effect modifiers.

WORD COUNT: 250

1.0 INTRODUCTION

Patellofemoral pain (PFP) is a prevalent and persistent knee condition [1 2] that affects approximately 1 in 20 teenagers and 1 in 10 adult women. [3-7] Despite receiving evidence-based treatments that are initially effective, more than one third of patients' still report persistent symptoms 12 months later [2] with approximately 25% reporting symptoms up to 20 years later.[8] It might be helpful clinically to know whether certain prognostic factors can identify patients with PFP who are at risk for a poor outcome. A review identified a number of prognostic factors for outcomes in those with PFP (e.g., age, pain severity, foot posture/motion), [9] only presented differences between groups at baseline, which are not helpful to the clinician wanting to determine the prognosis of a specific patient.

The complex and multifactorial nature of PFP leads to a heterogeneous clinical presentation.[10] A recent best practice guide recommended that treatment be tailored to each patient's presentation, but it did not provide direction for the clinician on how to individually tailor treatment.[11] Prognostic factors are patient characteristics that help to determine a specific outcome within a certain time period. [12 13] Treatment effect modifiers are patient characteristics that predict a successful outcome from a specific treatment. An evidence-based approach to individually tailor treatment requires the identification of treatment effect modifiers, because although prognostic factors help predict the likelihood of an outcome within a certain time period, they cannot predict the likelihood of an outcome after a specific treatment. [14]

To inform clinical practice and research related to PFP, the purpose of this systematic review was to determine which baseline patient characteristics were: (i) associated with a poor outcome (prognostic factors); or (ii) associated with a successful outcome after a specific treatment (treatment effect modifiers).

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2.0 METHODS

2.1 Search Strategy

The systematic review was conducted following the PRISMA guideline. [15] Electronic databases (Medline, Scopus, Embase, CINAHL, SPORTDiscus and Web of Science) were searched up to July 2016 for studies investigating conservative (non-surgical) treatments for PFP. Key search terms relating to PFP and other such synonyms used in all databases were adapted from similar search strategies. [10 16 17] Keywords used to narrow the search to the aim of the review were success*, factor*, predict*, charact*, prognos*. Searches were limited to human studies with no language restrictions (appendix 1). The protocol for the systematic review was not registered.

2.2 Eligibility

Studies were included if they had investigated: (a) participants diagnosed with PFP determined by clinicians based on the report of retro or peripatellar pain that was provoked by either a partial squat, stair ascent or descent and pain reported during palpation of peri-articular structures, and (b) an association between patient characteristics that were measured at the outset of the study and the outcome (status of the condition) at a later time (minimum period of 1 week). Only conservative (non-surgical) approaches were included. Studies were excluded if they included pain from

structures other than the patellofemoral joint, and other knee pathologies such as internal derangement, knee ligament insufficiency or patellar tendinopathy. Case reports or reviews of the literature were also excluded.

2.3 Review process
All identified studies were imported into Endnote X6 (Thomson Reuters, Carlsbad, California, USA) and duplicates removed. Two reviewers (MM & MSR) independently assessed study titles and abstracts for eligibility with a third reviewer (BV) available if necessary to resolve discrepancies. Where there was duplication or pooling of data from different trials, only the primary publication (the study of the highest relevancy to the purposes of this review as determined by all three reviewers) was included. Reference lists of all publications considered for inclusion were hand-searched recursively until no additional eligible publications were identified.

2.4 Quality assessment
Two reviewers (MM and MSR) independently assessed papers for quality. Any discrepancies were discussed to reach consensus, and if discrepancies remained, a third reviewer was consulted (BV). Study quality of all included studies was assessed using the Epidemiological Appraisal Instrument (EAI) [18] in a method used in previous reviews. [19 20] Items were scored as Yes (score = 2), Partial (score = 1), No (score = 0), Unable to determine (score = 0) of the applicable items. An average score was then calculated across all applicable items for each study (range 0-2). The EAI is a valid and reliable appraisal instrument for systematic reviews [21]

Studies that aimed to investigate predictors of outcome after a specific treatment were further evaluated for quality using a checklist for prescriptive, derivation-based clinical prediction rules (QUADCPR). [22] The QUADCPR was designed and developed using a 3-round Delphi process involving physicians, epidemiologists and physical therapists. It includes 23 items across 4 sections – (i) sample and participants (ii) outcome measure (iii) quality of tests and measures and (iv) statistical assumptions. Each item is scored yes, no, or unclear without generating a quantitative score. Two modifications were made to the QUADCPR for the purposes of this review. First, in accordance with the statement on Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) [23], an adequately powered study required at least 10 participants in the limiting sample size (group with least frequent outcome) for each variable analyzed as a potential predictor (Question 18). Second, in discussion with the corresponding author of the QUADCPR, a fifth section was added to assess whether outcomes are treatment effect modifiers - (v) quality of treatment approach. This section addressed the quality of the treatment approach using published recommendations on the preferred study methods for identifying treatment effect modifiers and subgroup effects.[14 24 25] An additional 4 questions were inserted into the checklist (Questions 24 -27) that addressed treatment explanation and implementation of the target treatment and comparator treatment.

2.5 Data Extraction and Analysis
Study details were extracted by MM and checked by MSR. Details extracted were: publication details, sample characteristics, participant demographics, study methods

including study design, outcome measures, any intervention(s), and the baseline factors studied. Study results were extracted by following the definitions for a successful outcome or poor outcome applied by each individual study. Outcome measures used per study are detailed in Table 2 (col. 4) and Table 3 (col. 3). Relationships between baseline predictors and a poor outcome (i.e., prognosis) were expressed as R^2, whereas baseline predictors and a successful outcome after a specific treatment were quantified by extracting positive likelihood ratios (LR+) and odds ratios (OR). Positive likelihood ratios indicate the probability of having a successful outcome if the identified predictor is present. Shifts in probability of a successful outcome are categorized as small and rarely important (LR+ 1-2), small but sometimes important (LR+ 2-5), moderate shift (LR+ 5-10) or large and often conclusive (LR+ >10). [26] Odds ratios measure the association between the exposure and an outcome (OR >1 higher odds; OR <1 lower odds). For studies that did not report OR, LR+ or post-test probability scores, authors were contacted and those indices were calculated from available data. Meta-analyses were performed where appropriate.

3. 0 RESULTS

3.1 Search results and critical appraisal of methods

The search retrieved 11629 citations, of which 7339 unique titles and abstracts were reviewed, with 59 papers identified for full text examination. Twenty-four studies met the eligibility criteria for quality assessment and data extraction, (figure 1) which evaluated 180 participant characteristics (appendix 2). The most frequently evaluated characteristics were age and sex (n=14 studies), knee pain duration (n=13), Q angle, body mass index, weight and height (n=8), sports participation (n=6) and navicular drop (n=5 studies). Twelve studies investigated patient characteristics associated with a poor outcome, and the remaining 12 studies investigated patient characteristics associated with successful outcome after a specific treatment.

Figure 1 PRISMA flow diagram

3.2 Quality assessment

Overall across all 24 studies, there was good conformity of the study aims, treatments, assessments and main findings on the EAI checklist. Very few studies reported adequate adjustment for covariates in the statistical analyses, blinding of observers or reporting of adverse events. There was also a lack of reporting reliability and validity of the main outcome measures used (see online appendix 3). Twelve studies investigated prognostic factors for a poor outcome (three randomized controlled trials, eight case series and one had no treatment), only one of the randomized trials [27] adjusted for treatment and reported it was not a confounder.

In addition to being evaluated for quality on the EAI, studies that investigated patient characteristics associated with successful outcome after a specific treatment were appraised under the QUADCPR checklist (n=12). Overall on the QUADCPR quality checklist, significant methodological limitations were identified with only one study using a control group. Only one study [28] had adequate statistical power with at least 10 participants in the limiting sample size (group with least frequent outcome) for each

potential predictor included in the statistical analysis. Even if a lower threshold of 5 participants in the limiting sample size for each potential predictor is used, [29] this was still the only study that had adequate statistical power. An issue with potential reporting bias was identified with only four [28 30-32] of the twelve studies administered outcome measures in a blinded fashion and in only three studies were the examining [28 30 33] or treating [30 32 34] clinicians blind to the outcome measures (table 1).

Table 1 Quality appraisal using a checklist for prescriptive, derivation-based clinical prediction rules (QUADCPR)

Questions	Barton 2011a	Barton 2011b	Crowell 2012	Huang 2015	Iverson 2008	Lan 2010	Lankhorst 2015	Mills 2012	Peng 2015	Rathleff 2015	Sutlive 2004	Vicenzino 2010
1. Setting and location reflective												
2. Inclusion and exclusion criteria												
3. Sample characteristics												
4. Prospective and consecutive sampling												
5. Outcome measure(s) defined												
6. Outcome measure reliability, validity and sensitivity to change												
7. Blinded outcome measure(s)												
8. Outcome measure defined (positive/ negative)												
9. Logical rationale for predictor test												
10. Predictor test was performed pre-treatment												
11. Predictor test and measures were explained in detail												
12. Predictor tests/ measures performed in a clinically consistent, acceptable, and appropriate method												
13. Examining clinicians blinded to the outcome measures												
14. Treating clinicians blinded to outcome measures												
15. Reliable predictor tests and measures used (>0.60 Kappa and or 0.70 ICC)												
16. Appropriate time intervals												
17. Equivocal or indeterminable results were reported												
18. Adequate sample powering (10 subjects in the limiting sample size for each potential predictor variable) *footnote												
19. First order interactions were assessed and reported												
20. The statistical significance of the model or "fit" was reported												
21. Confidence intervals of the regression analyses reported												
22. Irrelevant predictors removed prior to multivariate modeling												
23. Statistical results of the clinical prediction rule were reported using 95% CI												
24. Treatment/ intervention procedures are explained in detail												
25. Treatment/ intervention(s) were performed in a clinically consistent, acceptable, and appropriate method												
26. Comparator treatment/ intervention procedures are explained in detail												
27. Comparator treatment/ intervention(s) were performed in a clinically consistent, acceptable, and appropriate method												

Black shading = "Yes", Grey shading = "Unclear", White (no shading) = "No"

Inter-rater agreement between the quality assessors was 92% across all 13 papers.

*footnote: Modified in accordance with the TRIPOD statement [23] recommendation for a minimum of 10 subjects in the limiting sample size (i.e. those who experienced the least frequent outcome) for each potential predictor variable included in the analysis.

3.3 Patient characteristics associated with a poor outcome (prognosis)
Sixteen patient-reported and anatomical characteristics were associated with a poor outcome, with degree of association (e.g., R^2) ranging from 27 to 46% (table 2). The patient-reported characteristics were duration of PFP symptoms [27 35 36] bilateral symptoms, [37] higher frequency of pain occurrence, [38] older age, [39] female gender, [36] lower baseline Kujala knee pain score and function (Kujala scale and functional index questionnaire in [27]), poor health and low/middle education level. [37]

Anatomical characteristics associated with a poor outcome were swelling of the knee (self-reported by the participant in [37]), patellar hypermobility, [36] slower vastus medialis obliquus reflex response, [35] larger side to side differences in isometric quadriceps muscle strength, [40] smaller quadriceps cross sectional area on MRI and lower eccentric knee strength, [38] evidence of chondromalacia patella on MRI and a tibial tubercle lateral deviation > 14.6 mm relative to the trochlear groove. [41]

Table 2 Patient characteristics associated with a poor outcome (prognosis)

Author	Sample size (n)	Variables assessed (n)	Outcome measures	Univariate (p) or Multivariate (p)	Follow up	Prognostic variables for a poor outcome	Explained Variance (R^2)	Covariate	Intervention(s)	Trial Type
Blond and Hansen 1998 [36]	250	12	Pain resolution	Univariate (p<0.05)	5.7 yrs	Hypermobile patella >4month duration of symptoms Female	-	None specified	Advised to wear knee brace and VMO exercises: open and closed kinetic chain (Phase 1: non-loaded, phase 2: loaded exercises, phase 3: return to main athletic activity)	Retrospective case study
Collins et al 2010 [27]	179	11	1. Pain (VAS) 2. Kujala Scale 3. Functional Index Questionnaire	Univariate (p<0.01) then multivariate (p<0.01)	6 wks	1. High pain severity 2. Longer duration of symptoms, lower baseline Kujala score 3.Longer duration of symptoms, lower baseline Functional Index Questionnaire score	1. R^2 = 23% 2. R^2 = 40.1% 3. R^2 = 38.6%	Treatment group	Flat inserts - versus - foot orthoses – versus - physio exercises (patellar mobilization, patellar taping, VMO retraining, Hip ER retaining and hip and hamstring stretches) – versus - foot orthoses and physio exercises	Randomized Controlled Trial
					12 wks	1. Nil 2. Lower baseline Kujala score 3. Lower baseline kujala score	1. - 2. R^2 = 28% 3. R^2 = 22%			
					52 wks	1.Nil 2. Long duration of symptoms, lower baseline Kujala 3. Long duration of symptoms	1. - 2. R^2 = 29.5% 3. R^2 = 26.6%			
Kannus and Nittymaki 1994 [39]	49	22	1. Pain (VAS) 2. Lysholm scale 3. Tegner scale	Univariate (p<0.05) then multivariate (p<0.05)	6 wks	1. Older age 2. Older age 3. Older age	-	None specified	Rest, quadriceps strength, quadriceps stretch, cold pack (10mins) non-steroidal anti-inflammatory medication and intra-articular injections (n=33, 5x - 1x/week) of physiologic saline (n=17) or glucosamine (n=16)	Prospective cohort study
					26 wks	1. Nil 2. Older age 3. Older age				

Karlsson et al 1996 [42]	48	3	Patellofemoral joint evaluation scale	Univariate (p≤0.001)	11 yrs	No variables found	-	None specified	Quadriceps isometric activation. Straight leg rises with angle weights and inner range quad with ankle weights (30-0°)	Retrospective case-control study
Kastelein et al 2015 [37]	48	21	GROC - 7 point	Univariate (p<0.20) then multivariate (p<0.10)	52 wks	Low/middle education level Poor health Bilateral symptoms Self-report of a swollen knee	-	None specified	None	Prospective cohort study
Kettunen et al 2012 [43]	56	6	Kujala Knee Pain score	Univariate (p value not specified)	5 yrs	No variables found	-	None specified	Arthroscopic surgery – versus - home exercise program (8weeks)	Randomized Controlled Trial
Natri et al 1998 [40]	49	11	1. Pain severity (VAS) 2. Lysholm scale 3. Tegner Scale	Univariate (p<0.05) then multivariate (p<0.05)	7 yrs	Greater side to side isometric quadriceps muscle strength difference	-	None specified	Rest, quadriceps strength , quadriceps stretch, Non-steroidal anti-inflammatory medication & intra-articular injections (n=33, 5x - 1x/week) of physiologic saline (n=17) or glucosamine (n=16)	7 year Prospective cohort study
Nimon et al 1998 [8]	63	6	1. Pain resent 2. Pain severity 3. Analgesic use 4. Pain frequency 5. Sport restriction 6. Pain associated activities 5. Other symptoms	Univariate (p not specified)	16 yrs	No variables found	-	None specified	Physiotherapy and laster immobilization	Prospective cohort study
Pattyn et al 2012 [38]	40	21	1. Kujala Knee pain Scale 2. GROC – 5-point Likert scale	Univariate (p<0.05)	7 wks	Higher frequency of pain at baseline Smaller quadriceps muscle size Greater average eccentric peak torque at 60°/sec	$R^2 = 0.46$	None specified	Mobilization, neuromuscular coordination exercises, stabilization exercises, strengthening exercises, stretching, cardiovascular and home exercise program of neuromuscular coordination exercises	Prospective cohort study
Rathleff et al 2015 [44]	39	2	1. PPT localised 2. PPT distal 3. GROC – 7-point Likert scale	Univariate (p<0.05)	12 and 52 wks	No variables found	-	None specified	Patient education – versus - patient education and exercises therapy	Randomized controlled trial

Wittstein et al 2009 [41]	30	4	PT Responders: resolution of symptoms to the point that they required no further treatment PT Non-responders: continued to have PFP severe enough that they sought further treatment		8 wks	Evidence of chondromalacia patella on MR imaging Tibial tubercle deviation >14.6mm	-	None specified	Strengthening, stretching, footwear modification and Non-steroidal anti-inflammatory medication	Retrospective case-control (comparative) study
Witvrouw et al 2002 [35]	30	39	1. Kujala Knee Pain Scale 2. Manual test (Q-angle, muscle length, patellar glide) 3. Subjective assessments 4. Functional assessments		5 wks	Slower reflex response time (VMO) Longer duration of symptoms	-	None specified	No sports participation, no medication prescribed, no brace or tape, stretching exercises, strength exercises (Seated leg press, double or single one-third knee bend, stationary bike (10-15min @ 100W), rowing machine, step up and down (at pain free height), progressive jumping (3x1min)) and home exercise program to maintain strength	Prospective cohort study
					12 wks	Slower reflex response time (VMO) Longer duration of symptoms				

GROC = global rating of change, PPT= pressure pain threshold, VMO = Vastus medialis obliquus, VAS = visual analogue scale, *foot note: all variables are listed in appendix 2

3.4 Patient characteristics associated with a successful outcome after a specific treatment

Six different specific treatments were investigated; foot orthoses, [30 32 33 45-47] lumbopelvic manipulation, [34 48] patellar taping, [31] femoral nerve mobilization, [49] leg press exercise and stretching [28] and exercise therapy (consisting of static and dynamic exercises for the quadriceps muscles, flexibility and balance exercises) [50] (table 3). Twenty-two patient characteristics were reported to be associated with a successful outcome after a specific treatment. Studies defined a successful outcome using a predetermined amount of improvement in pain scores, questionnaire and/or a rating on a global rating of changes scale to stratify respondents into successful or unsuccessful outcomes.

Table *3* Patient characteristics associated with a successful outcome from a specific treatment

Author	Intervention	Comparator	Outcome measure	Sample (n)	Success (n)	Predictors to a successful outcome	Significance level (p)	Positive Likelihood Ratio (95% CI)	Odds Ratio (95% CI)
Barton 2011a [33]	Foot orthoses	Nil	5-pt GROC	60	14	Footwear motion control properties (weighted mean) >5.0 Usual pain <22.0/100mm (VAS) Ankle Dorsiflexion (knee flexed) <41.3° Reduced pain during single leg squat	0.05	1.9 (1.1–3.1) 2.5 (1.3–4.8) 1.5 (0.71–3.3) 3.0 (1.8–4.9)	
Barton 2011b [46]	Foot orthoses	Nil	5-pt GROC	26	7	Greater rearfoot eversion relative to the laboratory floor	0.05	-	-
Crowell & Wofford 2012 [34]	Lumbo-pelvic manipulation	Nil	11-pt NPRS 15-pt GROC.	44	25	Hip IR side to side difference >14° Ankle dorsiflexion (knee flexed) >16° Navicular drop >3mm No self-reported stiffness sitting >20 min Squatting (most painful activity)	0.05	0.76 (0.05, 11.39) 0.93 (0.78, 1.11) 1.52 (0.54, 4.31) 0.74 (0.46, 1.19) 0.82 (0.49, 1.37)	
Huang 2015 [49]	Femoral nerve mobilization	Nil	10cm VAS 15-pt GROC	51	28	Significant immediate efficacy Bilateral difference in hip extension angle of femoral slump test (>3°)	0.05	NA 5.11 (1.28-20.30)	
Iverson 2008 [48]	Lumbo-pelvic manipulation	Nil	11-pt NPRS 15-pt GROC.	49	22	Hip IR side to side difference >14° Ankle dorsiflexion (knee flexed) >16° Navicular drop >3mm No self-reported stiffness sitting >20 min Squatting (most painful activity)	0.05	4.9 (1.2, 20.8) 2.0 (1.0, 3.9) 1.91 (1.0, 3.6) 2.0 (1.1, 3.4) 2.3 (1.1, 4.7)	
Lan 2010 [31]	Patella taping	Nil	100mm VAS	100	66	Smaller Lateral Patellofemoral Angle Larger Q Angle Lower BMI	0.05	-	0.81 (0.70-0.95) 1.14 (1.03-1.26) 0.85 (0.75-0.98)
Lankhorst 2015 [50]	Exercise therapy (ET)	Usual care (UC)	Kujala scale 11-pt NPRS	131	At 3mth 26(ET) 21(UC) At 12 mth 36(ET) 30(UC)	Nil significant [a]	0.01	-	-
Mills 2012 [32]	Foot orthoses	Wait-and-see	6-pt GROC	40	9(FO) 1(W-S)	Foot orthoses: Mid-foot width difference >11.25mm [b]	0.05	3.9 (1.07-14.1)	
Peng 2015 [28]	Leg press and stretching	Nil	10cm VAS	43	24	Difference in patella tilt angle between maximal quadriceps contraction and quadriceps relaxed (measured on axial CT)	0.05	-	0.84
Rathleff 2015b [47]	Foot orthoses	Nil	PFP Severity Scale	23	12	Immediate decrease in the medial-to-lateral peak force after fitting the orthoses during drop jump task	0.05	-	-
Sutlive 2004 [45]	Foot orthoses and activity modification	Nil	15-pt GROC	50	27	Forefoot alignment ≥2° valgus Great toe extension <78° Navicular drop test ≤3mm	Uncertain	4.0 (0.7–21.9) 4.0 (0.7–21.9) 2.3 (1.3–4.3)	-

Vicenzino 2010 [30]	Foot orthoses		5-pt Likert GROC	42	17	Age >25 years Mid-foot width difference >10.96mm Height <165cm Worst pain <53.25/ 100mm (VAS)	0.05	1.9 (1.1 to 3.1) 3.0 (0.91 to 9.6) 4.9 (1.2 to 20.9) 1.5 (0.74 to 2.9)	-

GROC = global rating of change, PPT= pressure pain threshold, VMO = Vastus medialis obliquus, VAS = visual analogue scale, NPRS = Numerical Pain Rating Scale, a: Analysis of interaction used was a classification and regression tree approach, b: Analysis of interaction used was a liner regression modeling.

3.4.1 Foot orthoses

Fourteen predictors were univariately associated with a successful outcome after foot orthoses treatment across six studies. [30 32 33 45-47] Four predictors were static measures of the foot; these were 2° or more of valgus forefoot alignment, 78° or less great toe extension, 3mm or less navicular drop [45] and two studies reporting a mid-foot width difference between weight bearing and non-weight bearing greater than 10.96mm. [30 32] Two studies investigated foot movements during functional tasks. One study used 3-D kinematic analysis during gait to show those who had a successful outcome had a mean difference of 2.3° greater rearfoot eversion relative to the ground than those who reported an unsuccessful outcome. [46] The other study of a drop jump task reported those who had an immediate decrease in the medial-to-lateral peak foot loading went on to report improvements in pain and function after wearing foot orthoses for 12 weeks.[47] Two studies found baseline pain scores of usual pain less than 22.0 mm [33] and worst pain less than 53.25 mm [30] on a 100mm visual analogue scale predicted a successful outcome. One functional performance predictor was reduced pain during a single leg squat whilst wearing foot orthoses. [33] Ankle dorsiflexion range less than 41.3°, relative to the vertical, (measured as tibial inclination using a digital inclinometer placed anteriorly mid-tibia) during weight bearing ankle dorsiflexion with a bent knee also predicted a positive outcome. [33] The clinical utility of such a specific cut point has not been further studied or the finding replicated. Other demographic predictors reported were height less than 165 cm and age over 25 years. [30] In addition to the patient centric factors, those participants who wore footwear with reduced motion control properties, assessed using a footwear assessment tool, [51] were more likely to report a successful outcome when wearing an orthosis. [33]

Three predictors (height, forefoot valgus alignment, great toe extension) had a reported LR+ range of 4.0 - 4.9 [30 45] but the 95% confidence intervals for these predictors were large raising greater uncertainty on the precision of these relationships. Three predictors of success had LR+ range between 2.5 to 3.9 and narrow confidence intervals; with two studies identifying midfoot width difference from weight bearing to non-weight bearing foot posture of >10.96mm [30] and >11.26mm, [32] reduced pain during single leg squat while wearing a foot orthosis and usual pain <22/100mm visual analogue scale.

Two studies used multivariate analysis to evaluate a combination of predictors for clinical prediction rules for success after treatment by foot orthoses (table 4). Each study reported a different combination of four predictors, with a LR+ of 8.8 (95%CI 1.2-66.9) [30] and 11.1 (95%CI 2.7-46.9) [33] when three or more predictors were present, raising post-test probability of success to 85.4% and 78% respectively. These LR+ suggest a moderate to large and often conclusive shifts in probability of a successful outcome after foot orthoses treatment. No participants in either of the two studies presented with all four of the respective predictors (table 4).

Table 4 Derived Clinical Prediction Rules for a specific treatment

Study	Intervention	Follow-up (weeks)	Predictors within the rule	n of predictors	Success/ non-success (n)	Sensitivity (95%CI)	Specificity (95%CI)	Positive Likelihood Ratio (95% CI)	Posttest Success (%)
Barton 2011a [33]	Foot orthoses	12	Footwear motion control properties >5.0 Usual pain <22.0/100mm (VAS) Ankle Dorsiflexion (knee flexed) <41.3° Reduced pain during single leg squat	≥1 ≥2 ≥3 All 4	11/25 11/16 7/2 0/0	1.00 (0.74-1.00) 1.00 (0.74-1.00) 0.64 (0.35-0.85) 0	0.26 (0.14 - 0.42) 0.54 (0.38 - 0.70) 0.94 (0.81 - 0.98) 0	1.3 (1.1 - 1.6) 2.2 (1.5 - 3.1) 11.1 (2.7 - 46.9) 0	24 41 78 0
Crowell & Wofford 2012 [34]	Lumbo-pelvic manipulation	1	Hip IR side to side difference >14° Ankle dorsiflexion (knee flexed) >16° Navicular drop >3mm No self-reported stiffness sitting >20 min Squatting (most painful activity)	≥2 ≥3 ≥4 ≥5	- - - -	0.72 (0.54–0.90) 0.45 (0.23–0.67) 0.16 (0.02–0.30) 0.02 (0–0.07)	0.11 (0–0.24) 0.33 (0.14–0.52) 0.84 (0.68–1.01) 0.95 (0.85–1.0)	0.8 (0.6–1.1) 0.7 (0.4–1.2) 1.0 (0.3–4.0) 0.4 (0–10.5)	- - - -
Iverson 2008 [48]	Lumbo-pelvic manipulation	1	Hip IR side to side difference >14° Ankle dorsiflexion (knee flexed) >16° Navicular drop >3mm No self-reported stiffness sitting >20 min Squatting (most painful activity)	≥1 ≥2 ≥3 ≥4 all 5	0/11 5/11 8/1 5/0 2/0	0.91 (0.71, 0.99) 0.91 (0.71, 0.99) 0.68 (0.45, 0.86) 0.32 (0.15, 0.55) 0.09 (0.02, 0.31)	0.15 (0.04, 0.35) 0.56 (0.35, 0.75) 0.96 (0.81, 1.00) 1.00 (0.84, 1.00) 1.00 (0.84, 1.00)	1.1 (0.87, 1.3) 2.05 (1.3, 2.9) 18.4 (3.6, 105.3) Infinite (0.90, infinite) Infinite (0.31, infinite)	47 63 94 100 100
Vicenzino 2010 [30]	Foot orthoses	12	Age >25 years Mid-foot width difference >10.96mm Height <165cm Worst pain <53.25/ 100mm (VAS)	≥1 ≥2 ≥3 All 4	17/16 12/8 6/1 0/0	1 (0.77 to 1.0) 0.71 (0.44 to 0.89) 0.35 (0.15 to 0.61) -	0.36 (0.19 to 0.57) 0.68 (0.46 to 0.84) 0.96 (0.78 to 0.99) -	1.6 (1.2 to 2.1) 2.2 (1.1 to 4.2) 8.8 (1.2 to 66.9) -	52.7 59.5 85.4 -

IR = internal rotation; (VAS) = visual analogue scale

3.4.2 Lumbopelvic manipulation
Five predictors were identified using multivariate analysis and reported to be associated with a successful outcome after lumbopelvic manipulation. [48] A follow up study [34] on a different but similar sized PFP cohort failed to replicate the same five predictors reported by Iverson et al. [48]

3.4.3 Patellar taping
One study [31] reported three predictors of a successful outcome with patellar taping as described by McConnell. [52] After multivariate analysis, smaller lateral patellofemoral angle (an angle formed by the line between the femoral condyles and another line between the margins of the lateral facet of the patella) measured with radiographs in 30° of knee flexion, larger Q angle and a lower body mass index [31] were reported to be associated with a successful outcome. Larger Q angle was the only one of three reported predictors have an OR >1 (OR 1.14 95%CI 1.03-1.26).

3.4.4 Femoral nerve mobilization
One study [49] reported two predictors to be associated with a successful outcome after six sessions of femoral nerve mobilization. After multivariate analysis, significant immediate improvement after a femoral nerve mobilization and a bilateral difference of at least 3° in hip extension angle of the femoral slump test, which had a LR+ 5.1 (1.3-20.3), suggests a moderate shift in probability of successful outcome after femoral nerve mobilization.

3.4.5 Exercise
Two studies investigated predictors of successful outcome after exercise. One study compared exercise therapy to usual care and found no significant predictors of a successful outcome to exercise therapy. [50] One study evaluated a leg press training and lower limb muscle stretching exercise program. [28] Patellar tilt angle difference (PTA-d), which is the difference in patellar tilt angle in a quadriceps contracted (Qc) and a quadriceps relaxed (Qr) position measured on axial computed tomography, was associated with a successful outcome after a leg press strengthening and lower limb stretching program. [28] Those who had greater PTA-d (i.e greater realignment of the patella with quadriceps contraction) before beginning exercise treatment had greater reductions in pain after treatment. [28] The optimal cut-off value was −1.5° PTA-d (Qc−Qr) for the clinical discrimination of treatment success based on a minimum pain reduction of 1.5-cm on the VAS (sensitivity = 0.74, specificity = 0.71, LR+ 2.5).

4.0 DISCUSSION:
Our systematic review on PFP investigated baseline patient characteristics that were associated with a: (a) poor outcome (prognosis), or (b) successful outcome after a specific treatment (treatment effect modifiers) after more than one week. The review highlighted a large amount of non-significant association with a total of 180 patient characteristics being investigated by 24 studies. Twelve prognosis studies investigated 104 characteristics and identified 16 prognostic factors associated with a poor outcome. Twelve studies reported that only 22 out of 100 potential treatment effect modifiers were associated with a successful outcome after a specific treatment. However, the review

identified significant methodological limitations in all studies appraised with the EAI and modified QUADCPR tools. Of the 12 studies that investigated prognostic factors, only one study, a randomized controlled trial, [34] controlled for treatment and showed it was not a confounder. Of the 12 studies that investigated potential treatment effect modifiers, 11 did not have a control condition or a comparator treatment. It is therefore unclear whether the 22 baseline patient characteristics identified in these studies actually predict success following a specific treatment (treatment effect modifiers) or are just non-specific prognostic factors. As a result of these limitations, pooling and meta-analyses of the data were not warranted. Although definitive conclusions cannot be drawn until these methodological limitations are addressed, in order to make the best use of available evidence, our discussion will focus first on studies investigating prognostic factors for a poor outcome followed by studies that investigated potential treatment effect modifiers.

Prognostic factors are important in the decision making process and managing patient expectations. [53] Persistent PFP symptoms could have a negative impact on the physiological and psychological well-being of an individual with PFP. [1 54 55] Of the 12 studies that evaluated prognostic factors for a poor outcome, 16 characteristics were reported, but only five were investigated by more than three studies. Longer duration of knee pain, [27 35 36] older age, [39] greater usual pain severity and lower baseline anterior knee pain score [27] were factors of an unsuccessful outcome (table 5). Three of the five studies that evaluated duration of knee pain, one a large prospective study, reported a consistent finding of longer duration of pain (>4 months [35]) as an indicator of a poor outcome. Longer duration of symptoms as a poor prognostic indicator seems to be consistent across musculoskeletal conditions, [56] even in adolescents with knee pain.[1] It would appear prudent for clinicians to keep duration of symptoms in mind when consulting a patient with PFP. This prognostic factor should also be considered in guidelines and future research for the effective management/prevention of persistent PFP.

Table 5: Prognostic factors and potential treatment effect modifiers identified in this review.

		Modifiable with non-operative treatment	***Potentially modifiable***	***Unable to modify with non-operative treatment***
Factors associated with a poor outcome				
Prognosis	Clinically measurable	Swelling of knee (self-reported) [37] Lower Kujala score [27] Higher frequency of pain [38] Bilateral symptoms [37] Lower eccentric knee strength [38] Larger asymmetry in side-to-side isometric quads strength [40]	Low/middle education [37] Poor health [37]	Longer duration [27 35 36])] Older age [39] Female gender [36] Patellar hypermobility [36]
	Not standard clinical measurement	Smaller quads cross sectional area [38]	Slower VMO reflex response [35]	Tibial tubercle lateral deviation >14.6mm[41] Chondromalacia patella [41]
Factors reported to be associated with a successful outcome to a specific treatment				
Foot orthoses	Clinically measurable	Midfoot width difference > 11mm [30 32] Ankle dorsiflexion (knee flexed) <41° [33] Usual pain < 22/100mm (VAS) [33] Worst pain <53/100mm (VAS) [30] Reduced pain during single leg squat with orthoses fitted[33] Footwear motion control properties (weighted mean) <5[33]	-	Height < 165cm [30] Age > 25 yrs [30]
	Not standard clinical measurement	Greater rearfoot eversion relative to floor [46] Reduced medial-lateral peak force during drop-jump [47]		
Patellar Taping	Clinically measurable	Lower Body Mass Index [31]		Larger Q-angle [31]
	Not standard clinical measurement		Smaller lateral patellofemoral angle [31]	
Leg press & stretching lower limb muscles	Not standard clinical measurement		Difference in patellar tilt angle between maximum quadriceps contraction and quadriceps relaxed [28]	-

Twelve studies evaluated potential treatment effect modifiers associated with a successful outcome after a specific treatment with four conducting multivariate analyses to report clinical prediction rules for either foot orthoses, [30 33] or lumbopelvic manipulation. [34 48] A limitation of these single group studies identified in the QUADCPR appraisal was (a) the absence of an appropriate comparator intervention, [57] and (b) inadequate statistical power because limiting sample sizes were too small. Of the 12 studies that investigated potential treatment effect modifiers, 11 did not have a control condition or a comparator treatment. Lack of a control condition or a comparator treatment means there is no way to know that the outcome was necessarily due to the specific treatment. It is therefore unclear whether the baseline patient characteristics identified in these studies actually predict success following a specific treatment (treatment effect modifiers) or are just non-specific prognostic factors. The risk of spurious findings when overfitting or underfitting data to the limiting sample size was highlighted in a replication study of lumbopelvic manipulation for PFP [34] which used the same methods as the original study [48] but achieved contrasting results. Replication studies play an important role in predictive performance in a second, independent sample, especially when there are concerns about overfitting/underfitting data in the original study because of a relatively small limiting sample size. These studies need careful consideration in design that allow for an analysis of the interaction between treatment group and status on the prediction rule.

Foot orthoses were the most common treatment in studies that attempted to identify potential treatment effect modifiers (6 studies). One factor that was identified by two studies [30 32] and formed part of a multivariate clinical prediction rule, was midfoot width difference of greater than 11mm, reported by Mills et al. [32] This study was the only one of the 13 studies looking at treatment effect modifiers to use a control group (wait-and-see approach). [32] Mills et al [32] provide preliminary evidence that midfoot width difference might be useful at identifying those who might benefit from a foot orthosis, beyond natural history of the condition in the short term. This provides the clinician some useful information/evidence beyond any prognostic value of this foot characteristic.

Whilst single group studies cannot distinguish between treatment effect modifiers and non-specific prognostic factors, they can identify prognostic factors that could potentially be treatment effect modifiers. Rather appropriately the bulk of identified factors that might predict success with foot orthoses, were based at or around the foot. The two studies reporting clinical prediction rules for prescribing foot orthoses reported likelihood ratios that could signify a moderate to large and often conclusive shift in probability of a successful treatment. [26] The factors that are most likely to be clinically modifiable are ankle dorsiflexion (tibial inclination <41.3° from the vertical),[33] mid-foot width difference (>11mm) [30 32] and footwear motion control properties (weighted mean >5). [33] An interesting clinical examination finding that contributed to one of these clinical prediction rules was a positive treatment direction test, [58] which is essentially the immediate reduction in pain with a single leg squat on initial wearing of a foot orthosis. [33] Somewhat consistent with the report of a positive treatment direction test [33] is the finding of an immediate decrease in medial-to-lateral peak foot force with fitting a foot orthosis being associated with a successful outcome. [47] In another laboratory study, kinematic analysis found those with greater rearfoot eversion relative to the floor, would

also successfully respond to foot orthoses. [46] Taking the findings collectively, there appears to be a body of exploratory results from single group studies that suggests the ability of the reported clinically measureable and modifiable prognostic factors to be potential treatment effect modifiers to identify those who would be successful with foot orthoses (table 5). Further research is necessary to investigate clinically relevant and plausible prognostic factors from single group studies in appropriately designed clinical trials to test for their ability to be treatment effect modifiers. In particular, midfoot width difference should be further explored as a treatment effect modifier for foot orthoses compared to other treatments because it has been shown to predict success with foot orthoses when compared to no intervention.

In clinical practice, a positive finding of reproduction of symptoms with a femoral slump test, that reduced with neck extension, would reasonably direct the clinician to consider using femoral nerve mobilisations in patients who have PFP. Only one study reported clinical features that predicted success after femoral nerve mobilization treatment. [49]. In addition to the limitations of the single-group design, the authors used a modified testing protocol for the femoral slump test that is not easy to replicate in a timely manner in clinical practice. It is questionable the degree of confidence with which a clinician could determine a 3° difference from side to side as the authors did not report the error of this test measurement, so it is difficult to know if 3° exceeds measurement error. Nevertheless, further investigation of this treatment approach is warranted.

Patellar taping, strengthening and stretching exercises of the thigh and lower limb muscles are often recommended to treat PFP. [52] A study by Lan et al [31] reported that success following patellar taping was associated with lateral patellofemoral angle and Q angle. Peng et al [28] measured the difference in patellar tilt angle between relaxed and contracted states of the quadriceps, noting a greater difference i.e., greater realignment of the patella with a contracted quads with treatment success. Notably though, all these measures from single studies of patellar position were made with radiological imaging, which is not readily accessible in a typical clinical setting (table 5).

A series of important methodological issues were identified in the reviewed studies. Prognostic studies should ideally be prospective in design, [12] but in order to review all available studies that reported prognostic factors, weaker-designed retrospective studies were also included in this in review. Studies investigating predictors of a successful outcome after a specific treatment usually analyzed too many potential predictors for the limiting sample size. This increases the risk of over-fitting (or under-fitting) the data which can lead to the identification of predictors that are implausible and likely to perform poorly in new samples of patients [29] The absence of comparator interventions in studies investigating outcomes after a specific treatment make it difficult to differentiate between treatment effect modifiers and non-specific prognostic factors. Future studies should determine a sufficient limiting sample size to order to guide recruitment of an appropriate sample size. [25] Lastly, studies need to apply appropriate blinding where possible for participants and treating clinicians, but it is critical to blind investigators assessing the outcome to minimize false positives, or negatives, and potential biases.

5.0 CONCLUSION

This review of relationships between patient characteristics and treatment outcomes for PFP identified that methodological limitations such as the absence of a control/comparator group, or too many predictors for the limiting sample size, make it unclear whether the predictors reported actually modify treatment effects. Despite the limitations inherent in current research evidence we identified modifiable and measurable factors that have been studied so as inform hypotheses that may help in the clinical decision making process (table 5). Three prognostic studies of patient characteristics identified that persistence of PFP beyond 4 months should alert clinicians to increased risk of a poor outcome. Greater change in midfoot width from non-weight bearing to weight bearing was the only characteristic that had sufficient evidence for being a potential treatment effect modifier for a successful outcome after foot orthoses treatment. The LR+ suggested a small but sometimes important shift in probability of a successful outcome, and this characteristic did not predict short-term improvement in a control group who received no intervention. Adequately powered randomized trials that compare relevant treatments are needed so that treatment can be tailored to the individual patient.

CONTRIBUTORS

MM, MSR, AC, KC, RN, TM and BV conceived and designed the review. MM executed the search. MM, MSR and BV screened the articles, extracted the data and rated the methodological quality of the studies. MM, MSR, AC and BV performed the analysis and drafted the manuscript. MM, MSR, AC, KC, RN, TM and BV interpreted the data, revised the manuscript and approved the final version.

FUNDING

NHMRC program grant (#1091302) funded the review. MM is funded by the Australian Postgraduate Award.

COMPETING INTEREST

No competing interests to declare

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